How the Emerging NAFLD–NASH Crisis Underscores the Urgent Need for Better Diagnostics

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With NAFLD and NASH now affecting well over 1 billion people globally, the world needs better diagnostics to accurately detect liver disease in an affordable, easy-to-use and safe manner.

ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) and its inflammatory stage, Non-Alcoholic SteatoHepatitis (NASH), are now a global healthcare crisis, and the facts should frighten patients, healthcare providers and insurance companies alike.

NAFLD-NASH AT A GLANCE

- Affects over 1 billion people globally
- Fueled by obesity, diabetes and other factors, driving 30 million new NAFLD-NASH cases per year[1]
- Can progress asymptomatically to fibrosis, cirrhosis and cancer, and is overtaking hepatitis as the leading cause of liver transplants[2]
- Potentially tied to a higher risk of severe COVID-19 symptoms and longer SARS-CoV-2 viral shedding time[3]
- Drives direct annual healthcare costs of over $100 billion in the U.S. alone[4]
- Historically difficult to diagnose due to a lack of accurate and practical clinical tools
- Historically, no targeted treatments available besides weight loss, which has low compliance

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[1] Wong, MD, MS1 & Singal, MD, MS2,3, "Trends in Liver Disease Etiology Among Adults Awaiting Liver Transplantation in the United States, 2014-2019," *JAMA Network Open* 3, no. 2 (2020): 1-5.

[2] Wong &, Singal, "Trends in Liver Disease Etiology Among Adults Awaiting Liver Transplantation in the United States, 2014-2019," *JAMA Network Open* 3, no. 2 (2020): 1-5.

[3] Ji, Qin, Xu, Zhang, Cheng, Wang, Lau, "Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study," Journal of Hepatology 73, no. 2 (2020): 451–53.

[4] Z. Younossi, D. Blissett, R. Blissett, Henry, Stepanova, Y. Younossi, Racila, Hunt, Beckerman, "The Economic and Clinical Burden of Nonalcoholic Fatty Liver Disease in the United States and Europe," *Hepatology* 64, no. 5 (2016): 1577-86.

Against this grim backdrop, there also lies hope and opportunity. With a rich pipeline of NAFLD-NASH drugs in Phase II-III trials[5] and the first NAFLD-NASH drugs starting to reach commercial approval (e.g., Zydus-Cadila's Saroglitazar, March 2020)[6] an opportunity exists to develop higher-value and more practical diagnostic tools to screen the large population of NAFLD-NASH sufferers and monitor the efficacy of expanding treatment options.

This paper seeks to assess the shortcomings and merits of current and emerging NAFLD-NASH diagnostic technologies on two criteria: Diagnostic Value (their ability to correctly detect disease) and Accessibility (their affordability, ease-of-use and safety).

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DISCUSSION

Non-alcoholic Fatty Liver Disease (NAFLD) and its inflammatory form, Non-Alcoholic SteatoHepatitis (NASH), are rooted in an unhealthy accumulation of fat in the liver. Anything over 5%-6% hepatic steatosis (liver fat) is above what is deemed to be normal/healthy. Excess liver fat can lead to inflammation of the liver (NASH), fibrosis (scarring of the liver), cirrhosis (liver cell death), and liver cancer.

NAFLD-NASH are referred to as silent killers because they often don't noticeably manifest themselves until it is too late. In fact, NAFLD-NASH is on track to overtake hepatitis as the leading root cause of liver transplants this decade.[7] The direct medical costs of managing NAFLD-NASH are over $100 billion annually.[8]

Accurately and easily measuring liver fat is key to solving this global health crisis.

THE CURRENT STATE OF MEASURING HEPATIC STEATOSIS (LIVER FAT)

There are several tools available today to help clinicians assess and monitor the progression of early stage liver disease. Unfortunately, none have historically achieved the balance of high diagnostic value and high patient accessibility, which are essential to managing a population of 1+ billion NAFLD-NASH

[5] clinicaltrials.gov

[6] Zydus Cadila, "Zydus Announces World's First Drug for the Treatment of Non-Cirrhotic NASH," *PRNewswire* (2020).

[7] Yuval A. Patel,1 Carl L. Berg,1 and Cynthia A. Moylan, Nonalcoholic Fatty Liver Disease: Key Considerations Before and After Liver Transplantation, Digestive Diseases and Sciences (61), January 2016

[8] Z. Younossi, D. Blissett, R. Blissett, Henry, Stepanova, Y. Younossi, Racila, Hunt, Beckerman, "The Economic and Clinical Burden of Nonalcoholic Fatty Liver Disease in the United States and Europe," *Hepatology* 64, no. 5 (2016): 1577-86.

sufferers, growing at 3% per year.[9] To put that growth rate into perspective, it equals 30 million new cases of NAFLD-NASH added each year, which is more than the entire population of Australia.

A worthwhile framework to assess the relative strengths and weaknesses of liver fat measurement technologies is to rank them along two axes: Diagnostic Value and Accessibility.

Diagnostic Value: How capable is the technology in detecting and analyzing hepatic steatosis for the assessment and monitoring of NAFLD-NASH? Capability metrics include:

- Sensitivity: The percentage of people correctly identified as HAVING hepatic steatosis above a reference threshold (e.g., 6% liver fat)
- Specificity: The percentage of people correctly identified as NOT HAVING hepatic steatosis above a reference threshold (e.g., 6% liver fat)
- AUROC (Area Under Receiver Operator Curve): Summarizes the overall diagnostic accuracy of the test, measuring the relationship between sensitivity and specificity across a range of reference thresholds (e.g., liver fat threshold of 4%, 6%, 10%, 15%, 25%, etc.)

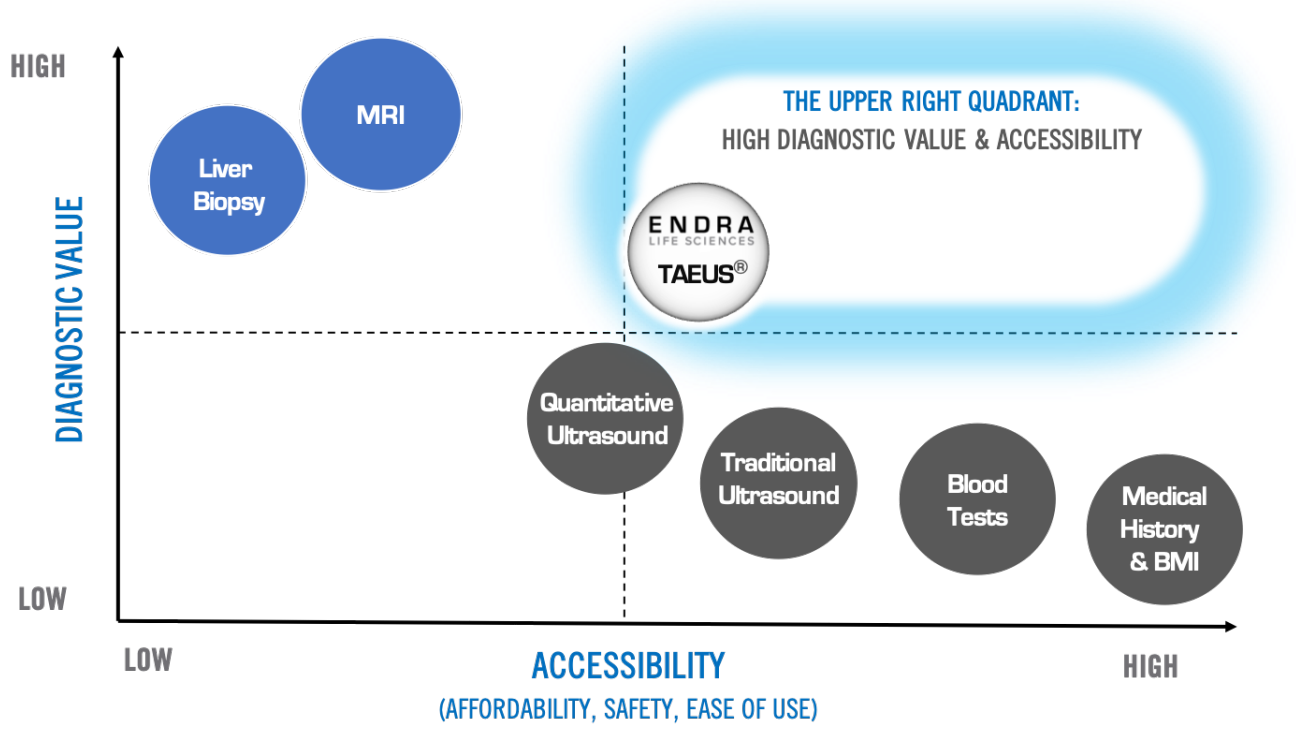
Accessibility: How globally available is the technology to screen and help manage 1+ billion people affected by NAFLD-NASH?

- How affordable is the technology to buy and use?
- How safe is the technology for patients (e.g., surgical risk) and operators?
- How easy is the technology to learn and use? Can it be deployed in a range of clinical settings (e.g., exam rooms, patient bedside)? Does it require advanced training to use (e.g., surgical training, radiological exam interpretation)?

Diagram 1 (page 4) visually illustrates how tools like MRI and liver biopsy have high diagnostic value, but relatively poor accessibility profiles, while other tools (blood tests, ultrasound) are generally accessible, but fall short in their relative diagnostic value.

[9] Shetty, MD & Syn, MD, PhD, "Health and Economic Burden of Nonalcoholic Fatty Liver Disease in the United States and Its Impact on Veterans," *Federal Practitioner* 36, no. 1 (2019): 14-19.

Diagram 1: Tools For Measuring Hepatic Steatosis (Liver Fat) to Assess & Monitor NAFLD-NASH



Source: ENDRA Life Sciences' assessment of relative position of key technologies

Let's take a closer look at the merits and drawbacks of each technology, and what the future holds.

LIVER BIOPSY & THE ROLE OF ARTIFICIAL INTELLIGENCE (AI)

Liver biopsy has been the historical standard for measuring NAFLD-NASH and advanced liver diseases such as fibrosis, cirrhosis and cancer. Biopsy of the liver involves a clinician inserting a 14-18 gauge needle between a patient's ribs, 2-3cm into the liver, and extracting a sample of the liver tissue.[10]

As an invasive and painful surgical procedure with risks (e.g., internal hemorrhage and even death from gallbladder perforation), biopsy is not a practical tool for everyday clinical practice. The "Accessibility" factor of liver biopsy – in terms of safety and ease-of-use – is poor.

[10] Vijayaraghavan, David, Bermudez-Allende, Sarwat, "Imaging-guided Parenchymal Liver Biopsy: How We Do It," *Journal of Clinical Imaging Science* 1, no. 30 (2011).

There is also growing scrutiny on the Diagnostic Value of liver biopsy for NAFLD-NASH patients. First, there is sampling risk, in that a biopsy only takes a small sample (approximately 1/50,000th) of the liver, which can lead to missing heterogeneously-deposited liver fat. Second, because of the complex cellular structures that develop as a result of NAFLD-NASH, a biopsy is subject to human pathologist interpretation error. Two pathologists may interpret the same liver biopsy differently, yielding different measures of hepatic steatosis. AI holds some promise to reduce the potential errors of human interpretation (by augmenting — not replacing — pathologists), but the surgical risk and pain of liver biopsy will keep it outside the realm of consideration for daily NAFLD-NASH clinical practice.

BLOOD TESTS & BIOMARKERS

There are a number of blood tests (a.k.a. biomarkers) currently in use or under investigation. For example, measurement of liver enzymes, such as Alanine Transaminase (ALT) and Aspartate Transaminase (AST), can help inform the causes of liver damage or hepatotoxicity.[11] Other blood tests in use include the BARD Score, NAFLD Activity Score, and ELF tests. New algorithm-based blood tests are also being developed, including some that measure up to eight different variables to derive a measure of liver health.

Blood tests offer varying degrees of sensitivity and specificity in measuring hepatic steatosis; for instance, ALT blood tests can achieve AUROC measures of 0.88, sensitivity of 0.91 and specificity of 0.77.[12] They can be helpful when combined with patient medical histories, body mass index (BMI) and non-invasive technologies (e.g., ultrasound). However, these combined technologies do not directly and rigorously measure fat deposited in the liver. Rather, they enable clinicians to "triangulate" estimates of hepatic steatosis. Blood tests get clinicians "in the ballpark," but not close enough to precisely measure and monitor treatment of NAFLD-NASH.

Several blood tests are still under development and more data is needed to ascertain their diagnostic value. Some Phase III NASH drug trials are including blood tests as a secondary test (supplementing biopsy) as a way to better understand their sensitivity and specificity.

Clinicians and drug researchers need a liver hepatic steatosis measurement tool that has both high Diagnostic Value and high Accessibility. Basic blood tests have achieved a good level of Accessibility,

[11] Nyblom, Berggren, Balldin, Olsson, "High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking," *Alcohol Alcohol* (2004): 39 (4): 336–9. Nyblom, Björnsson, Simré, Aldenborg, Almer, Olsson, "The AST/ALT ratio as an indicator of cirrhosis in patients with PBC," *Liver Int* (2006): 26 (7): 840–5. Gopal & Rosen, "Abnormal findings on liver function tests. Interpreting results to narrow the diagnosis and establish a prognosis," *Postgrad Medical* (2000): 107 (2): 100–2, 105–9, 113–4.

[12] Lemoine; Assoumou; De Wit. Diagnostic Accuracy of Noninvasive Markers of Steatosis, NASH, and Liver Fibrosis in HIV-Monoinfected Individuals at Risk of Nonalcoholic Fatty Liver Disease (NAFLD): Results From the ECHAM Study. JAIDS Journal of Acquired Immune Deficiency Syndromes. 80(4):e86-e94, April 1, 2019.

but unfortunately haven't yet achieved the necessary level of diagnostic rigor for measuring liver fat in NAFLD-NASH at its early stages when it is most treatable.

MAGNETIC IMAGING RESONANCE (MRI)

MRI (specifically MRI Proton Density Fat Fraction, or MRI-PDFF) is now largely recognized as the best-in-class measurement tool for NAFLD-NASH. MRI's Diagnostic Values for hepatic steatosis are strong:

- Sensitivity of 0.9[13]
- Specificity of 0.93[14]
- AUROC of 0.98[15]

Unfortunately, MRI has clear drawbacks in terms of Accessibility, which make it a poor choice to screen and manage 1 billion people with NAFLD-NASH:

- MRIs are expensive. A typical MRI costs $2M-$3M to acquire and over $150K/year to maintain.
- Few MRIs are available on a global basis. Only approximately 36,000 MRI systems exist globally[16] (compared to over 1 million ultrasounds) and only a portion of these MRIs are high-field systems capable of performing liver fat measurements. Over half of the world's MRIs are in the U.S. and Japan.
- MRIs require highly trained technicians and radiologists to operate and interpret exams.
- MRIs weigh 5+ tons and are anchored in magnetically-shielded rooms. They cannot be deployed to the front lines of NAFLD-NASH patient care: primary care physician offices or patient bedsides.
- MRIs are slow and the patient experience can be uncomfortable. A typical MRI liver scan takes 20 minutes, not including radiological reading time. MRIs are cramped, patients are required to hold their breaths at various intervals and MRIs generate loud noises (110db+) as their magnetic coils align, necessitating that patients wear earplugs.
- MRI's high magnetic fields may also be unsuitable for patients with cardiac pacemakers, metal orthopedic implants and large tattoos. (Note: Some tattoo inks contain magnetic pigments that can heat up during an MRI exam.)

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[13] Imajo, Kessoku, Honda, Tomeno, Ogawa, Mawatari, Fujita, Yoneda, Taguri, Hyogo, Sumida, Ono, Eguchi, Inoue, Yamanaka, Wada, Saito, Nakajima, "Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography," *Journal of Gastroenterology* 150, no. 3 (2016): 626-37.

[14] *Journal of Gastroenterology* (2016): 626-37.

[15] *Gastroenterology* (2016): 626-37.

[16] Ogbole, Adeyomoye, Badu-Peprah, Mensah, "Survey of magnetic resonance imaging availability in West Africa," *The Pan African Medical Journal* 30, no. 240 (2018).

As a result of these drawbacks, MRIs are rarely used in clinical practice for the screening of NAFLD-NASH alone. Their use is typically reserved for diagnosing more advanced diseases like cirrhosis or hepatocellular carcinoma (liver cancer).

ULTRASOUND: TRADITIONAL AND QUANTITATIVE VARIANTS

The need for non-invasive and lower cost tools has encouraged the development of other imaging techniques, like ultrasound elastography, with a higher Accessibility profile. While these ultrasound-based techniques are proving useful in assessing later stage liver disease progression like fibrosis, which stiffens the liver and changes the tissue echo signature of ultrasound, these technologies have historically suffered from insufficient sensitivity or specificity to be useful in the more complex tissue-composition analysis needed for early stage NAFLD-NASH assessment.

Traditional ultrasound, often referred to as B-mode (brightness mode) ultrasound, yields a 2D grayscale image of organs and tissues. It is widely used for the screening of liver disease, and allows clinically trained personnel to subjectively estimate fatty infiltration in the liver. Traditional ultrasound ranks high on the Accessibility score since it is broadly available, non-invasive, relatively low cost and does not expose patients to ionizing radiation.

However, traditional ultrasound has a low Diagnostic Value rating for the detection of mild to moderate steatosis (typically defined as 5% to 20%), with reported sensitivities in the 0.61 to 0.65 range, compared to 0.90 to 0.93 for MRI.[17]

This leaves an important clinical "blind spot" of steatosis measurement below 20% infiltration, when the disease can more easily be reversed, or to confirm when therapies or lifestyle changes have succeeded in lowering steatosis below the 20% level. Beyond the limited measurement ability of traditional ultrasound for mild-to-moderate hepatic steatosis, some patient conditions such as abdominal gas, obesity and liver fibrosis can further reduce the accuracy of the technology.[18]

Quantitative ultrasound tools, offered by a range of companies under assorted brand names, encompass ultrasound alternatives and calculations including elastography, backscatter coefficient, attenuation parameter and speed-of-sound estimations. These technologies have demonstrated a range of quantitative capabilities, ranging from poor to good in measuring hepatic steatosis.

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[17] Andre, Bernstein, Costa, Erdman, Fereirra, Gamst, Han, Heba, Lin, Loomba, O'Brien Jr, Paige, Sirlin, Wolfson, Valasek, "A Pilot Comparative Study of Quantitative Ultrasound, Conventional Ultrasound, and MRI for Predicting Histology-Determined Steatosis Grade in Adult Nonalcoholic Fatty Liver Disease," *American Journal of Roentgenology* 208, no. 5 *(2017):* 168-77.

[18] Ferraioli & Monteiro, "*Ultrasound-based techniques for the diagnosis of liver steatosis," World Journal of Gastroenterology* 25, no. 40 (2019): 6053–62.

- Sensitivity: 0.75 - 0.87[19]
- Specificity: 0.70 - 091[20]
- AUROC: 0.70 - 0.95[21]

Unfortunately, even the most promising of these technologies suffer from a range of Accessibility limitations, including cumbersome procedure workflow and user training (e.g., backscatter coefficient calculations usually require a reference phantom to adjust for measurement variability), high inter-operator variability and large overlaps in measurement accuracies of adjacent hepatic steatosis grades. The steatosis measurement capabilities of these quantitative ultrasound technologies are also susceptible to complicating factors like obesity and fibrosis, which are fairly common comorbidities in the NAFLD-NASH population.[22]

Finally, while these quantitative ultrasound technologies are generally safe and deployable closer to the patient than an MRI, they are typically available only in expensive standalone systems or as features in high-end ultrasound platforms costing more than $100,000. This price point typically puts quantitative ultrasound technologies out of easy reach for small clinical practices and "above the capital expense" line in many cost-constrained healthcare systems.

Traditional ultrasound and its quantitative variants fall short of achieving an optimal balance of Diagnostic Value and Accessibility for NAFLD-NASH hepatic steatosis measurement.

So, does anything approach the sweet spot for Diagnostic Value and Accessibility for hepatic steatosis measurement? Yes.

THERMOACOUSTIC ENHANCED ULTRASOUND (TAEUS®): A FIRST STEP INTO THE UPPER RIGHT QUADRANT OF THE DIAGNOSTIC VALUE / ACCESSIBILITY MATRIX

Unlike traditional and quantitative ultrasound, which pulse sound waves into tissues and generate return sound waves (sound in, sound out), ENDRA Life Sciences' TAEUS technology is a proprietary

[19] Lin, *Clinical Gastroenterology & Hepatology* 13 (2015). Andre, Bernstein, Costa, Erdman, Fereirra, Gamst, Han, Heba, Lin, Loomba, O'Brien Jr, Paige, Sirlin, Wolfson, Valasek, *American Journal of Roentgenology* 208 no. 5 (2017): 168-77. Causey, *Journal of Hepatology* 67, no. 4 (2018). Eddowes, Deeks, Newsome, "Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease," *World Journal of Gastroenterology* 156, no. 6 (2019): 1717-30.

[20] *Clinical Gastroenterology & Hepatology* 13 (2015). *American Journal of Roentgenology* 208 no. 5 (2017): 168-77. *Journal of Hepatology* 67, no. 4 (2018). *World Journal of Gastroenterology* (2019).

[21] *Clinical Gastroenterology & Hepatology* (2015). *American Journal of Roentgenology* (2017). *Journal of Hepatology* (2018). *World Journal of Gastroenterology* (2019).

[22] Ferraioli & Monteiro, "Ultrasound-based techniques for the diagnosis of liver steatosis," *World Journal of Gastroenterology* 25, no. 40 (2019): 6053–62.

hybrid which pulses radiofrequency (RF) waves into tissues - similar to an MRI - which in turn generate unique sound waves out like an ultrasound (RF in, sound out).

While the amount of RF energy deposited in tissue during a TAEUS liver exam is extremely small, similar to an iPhone or approximately 1/10,000th the energy deposited by an MRI, ENDRA has succeeded in decoding the thermoacoustic signatures (differential RF absorption and sonic signal patterns) of different tissue *types* (e.g., fat vs. muscle vs. blood), *functions* (e.g., tissue perfusion) and *states* (e.g., tissue temperature variations) in ways traditional or quantitative ultrasound cannot.

The first clinical application of TAEUS, leveraging TAEUS' tissue differentiation capabilities, is quantifying fat in a volume of tissue to aid in the management of NAFLD-NASH. ENDRA's initial in-human feasibility study yielded very promising Diagnostic Value measures with sensitivity, specificity and AUROC in the clinically relevant range, outperforming the majority of other non-invasive technologies, except for MRI[23] (see Diagram 2, page 10):

- Sensitivity: 0.88[24]
- Specificity: 0.82[25]
- AUROC: 0.91[26]

From an Accessibility perspective, TAEUS offers several advantages, including:

- Point-of-care deployability in a standard clinical exam room
- Relatively low price of approximately $50,000
- Fast and non-invasive liver fat exams: Each TAEUS scan takes approximately 1.5 seconds.
- Ease of use, leveraging the established clinical workflow of ultrasound

Are TAEUS' results as good as an MRI? No. But they don't need to be to adequately meet the diagnostic needs of the market. More specifically, clinicians typically reference an AUROC of 0.9 (90%) or higher as the threshold above which diagnostic tools achieve the highest clinical value, and ENDRA's feasibility study results are already above the 0.90 AUROC threshold.[27]

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[23] ENDRA, "A First Clinical Feasibility Study Employing Thermoacoustics to Estimate Liver Fat Fraction as Determined by MRI-PDFF" (2019): 1-4.

[24] ENDRA, "A First Clinical Feasibility Study" (2019).

[25] ENDRA, "A First Clinical Feasibility Study" (2019).

[26] ENDRA, "A First Clinical Feasibility Study" (2019).

[27] Mandrekar, PhD, "Receiver Operating Characteristic Curve in Diagnostic Test Assessment," *Journal of Thoracic Oncology* 5, no. 9 (2010): 1315-16.

Addressing the global pandemic of NAFLD-NASH cannot depend on a Ferrari-like tool (i.e., MRI), which most of the world cannot afford and is too slow and complicated to scan over 1 billion people. Rather, the world needs a high-quality tool with a balance of high Diagnostic Value and high Accessibility. TAEUS shows strong promise to achieve this objective.[28]

ENDRA still has work to do, including ongoing refinements to the hardware and software algorithms to improve the precision and sensitivity of the TAEUS liver device. To that end, ENDRA is planning to gather more data from evaluation sites such as the Medical College of Wisconsin (MCW), the University of Pittsburgh Medical Center (UPMC) and Rocky Vista University. Over time, ENDRA expects the additional data to help refine the TAEUS system and in turn, improve device design, as well as sensitivity and specificity ratings, which will ultimately enhance its overall accessibility and diagnostic value.

Diagram 2: Relative Performance of Hepatic Steatosis Measurement Tools

Liver Fat (Steatosis) Test	AUROC[1]	Sensitivity[2]	Specificity[3]	Diagnostic Value	Accessibility (Affordability, Safety, Ease-of-Use)	Other Considerations
Liver Biopsy	Historical Gold Standard for NASH Diagnosis			++	—	• Measurement variability due to pathology interpretation • Invasive. Requires surgical training.
Blood Tests (E.g., ALT) Lemoine, 2019 (J Acquir Immune Defic Syndr; 80(4)	0.88	0.91	0.77	—	+	• Low relative AUROC & specificity vs. other tests • Susceptible to non-NASH related diseases
Magnetic Resonance Imaging (MRI) Imajo, 2016 (Gastroenterology.150(3)	0.98	0.90	0.93	+++	—	• Becoming Gold Standard for research studies • Not practical for daily clinical practice. Costs $2M–$3M. • Slow & Complex, not point-of-care. Limited access. • Patient restrictions; hip replacements, obesity, tattoos....
Thermo Acoustic Enhanced Ultrasound (TAEUS®) ENDRA, 2019 (Roberts Feasibility Study, endrainc.com)	**0.91**	**0.88**	**0.82**	++	+++	• **Ease of use: ~15 mins training. 1.5 secs/scan.** • **Point-of-care. Works with any B-mode ultrasound.** • **Low cost: ~$50K** • **Strict quantitative measurement. Accurate, repeatable**
Qualitative Ultrasound: B-Mode Paige, 2017(AJR; 208)	0.81	0.89	0.70	—	++	• Broadly available, easy to use, point-of-care and safe. • Not recommended for low to medium fat level (<25%) • High level of training. Variable results, operator dependent
Quantitative Ultrasound: Backscatter, Attenuation, Elastography Lin, 2015 (Clinical Gastroenterology & Hepatology;13) Paige, 2017(AJR; 208) Causey 2018 (Hepatology, 67(4) Eddowes, Deeks, Newsome 2019 (Gastroenterology)	0.70 - 0.95	0.75 - 0.87	0.70 - 0.91	+	+	• Varied AUROC, sensitivity & specificity • Cumbersome techniques, some require use of phantom • Expensive, high level of training • Variable results, Operator dependent

[1] **AUROC** (Area Under Receiver Operator Curve): Measures the relationship between sensitivity and specificity as the Reference threshold changes (E.g., MR liver fat threshold of 6%, 10%, 15%, Etc).
[2] **Sensitivity**: The percentage of people correctly identified as having liver fat above the reference threshold (E.g., 6%).
[3] **Specificity**: The percentage of people correctly identified as NOT having liver fat above the reference threshold (E.g., 6%).

CLOSING THOUGHTS: THE GROWING OPPORTUNITY FOR IMPROVED DIAGNOSTICS IN THE NAFLD-NASH THERAPEUTIC RESEARCH SECTOR

In parallel to the clinical patient applications, there is a clear opportunity for better steatosis measurement tools at pharmaceutical companies and clinical research organizations (CROs) conducting NAFLD-NASH clinical trials.

[28] TAEUS has received CE Mark approval in Europe. It is not yet approved by the FDA.

These pharmaceutical companies and CROs depend on biopsy or MRI to screen-in and monitor the efficacy of their NAFLD-NASH therapies in human study subjects.

This poses two challenges:

1. People are not easily inclined to become research biopsy "pin cushions," causing delays in recruitment.
2. MRIs, as previously discussed, are slow and expensive. According to a 2018 JAMA report, clinical trials (of all kinds) cost a median of $41,117 ($31,802 - $82, 362) per patient and $3,562 ($2,583 - $4,682) per patient visit.[29]

Therefore, a pressing need exists for a more practical NAFLD-NASH steatosis measurement tool that enables more timely enrollment and monitoring of study subjects and generates financial savings from fewer MRI research scans (estimated to range from $3,000 -$5,000 per NAFLD-NASH MRI scan).

Biopsy, MRI, blood tests and the panoply of ultrasound derivatives cannot achieve the desired balance. They are either too impractical (low accessibility) or insufficiently rigorous diagnostically.

In contrast, ENDRA's TAEUS may offer a promising cost-effective, rapid and rigorous steatosis measurement tool that could save the NASH-NAFLD research segment time and money – even if TAEUS is introduced only as an adjunct tool to help screen-in subjects and occasionally monitor them between MRI scans.

With the commercialization of TAEUS now underway in Europe, ENDRA is taking an important first step to change this paradigm and meet the critical need for better diagnostic tools in the NAFLD-NASH market.

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[29] Anderson, Moore, Zhang, "Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016," *JAMA Internal Medicine* 178, no. 11 (2018): 1451-1457.